Functional Connectivity in Internally and Externally Oriented Networks: A Resting-State Corpus Callosum Agenesis Study

by

Lalaine Rose Dungca

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Graduate Supervisory Committee:

Corianne Rogalsky, Chair
Blair Braden
Sydney Schaefer

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ABSTRACT

The corpus callosum is a core white matter structure that sits at the center of the brain, playing a role in both interhemispheric communication and the inhibition of hemispheric activity to promote lateralization. Structural connectivity is thought to underlie functional connectivity (FC), but cases of structural brain abnormalities allow for a better understanding of this relationship. Agenesis of the corpus callosum (AgCC) is a condition in which an individual is born without a corpus callosum. These individuals provide a unique opportunity to investigate ways in which the brain adapts its functional organization to the lack of interhemispheric structural connectivity, thereby providing unique insights into brain network organization within and between the two cerebral hemispheres. The present study uses resting-state functional magnetic resonance imaging (fMRI) to compare the network connectivity of an individual with AgCC without any significant comorbidities to a control group of neurotypical adults ($n=30$). Potential differences of FC within the default mode network and frontoparietal network, as well as FC between these networks and bilateral language networks were examined. The AgCC individual displayed significantly higher FC within the frontoparietal network ($t(29)=1.84$, $p<0.05$) and significantly lower FC between the default mode network and the right ventral language stream ($t(29)=-1.81$, $p<0.05$) compared to the control group. Further analyses suggest that the right hemisphere’s frontoparietal network is driving the significant difference between the case study and control group in the frontoparietal network. The stronger FC of the frontoparietal network may represent a compensatory strategy used to support lower overall levels of default mode network and dual stream language network connectivity. Overall, the findings suggest that decreased

interhemispheric structural connectivity may lead to increased compensation via attention networks such as the frontoparietal network, and decreased right hemisphere language network involvement.

TABLE OF CONTENTS

CHAPTER Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

The corpus callosum sits at the center of the brain as its largest white matter structure, connecting the two hemispheres through over 190 million axons (Fitsiori et al., 2010). Whether the corpus callosum plays an excitatory or inhibitory role in interhemispheric interaction is still debated (Mancuso, et al., 2019). One side of the debate holds that the corpus callosum plays an excitatory role by prompting informational transfer, while the other holds that one hemisphere may at times work to inhibit the other (i.e., functional lateralization) (Mancuso et al., 2019). As both of these perspectives have been supported by numerous studies, it is likely that the structure can effectively both integrate and segregate information based on the task at hand. Past literature has agreed that the corpus callosum is far from a passive structure, but an active contributor to cognition and task execution (Bloom & Hynd, 2005). Recent developments in functional neuroimaging provide an insightful way to investigate the role of the corpus callosum in large scale brain networks that are involved in a wide array of cognitive functions critical to higher-order skills such as language and attention. In the present study, I will investigate core brain networks, and examine their potential alterations, in a case study of an individual without a corpus callosum (e.g. agenesis of the corpus callosum).

1.1 Agenesis of the Corpus Callosum and Brain Activity

Our knowledge about the corpus callosum as a core structure both functionally and structurally raises the question about how the brain would function in the case of agenesis of the corpus callosum (AgCC), or the complete or partial absence of the corpus callosum (Paul et al., 2007). The present study will investigate the functional connectivity (FC) of core brain networks in a normally functioning adult male with AgCC. Although it may be expected that in the absence of this prominent structure, interhemispheric FC would be disrupted, findings are conflicted. Patterns of regional intrahemispheric connectivity in AgCC patients have shown both increases and decreases in synchronized neural signals (Mancuso et al., 2019). This current study will investigate FC of two opposing networks: the default mode network and the frontoparietal network. Furthermore, it will examine possible FC differences between these networks and the dual stream language network. Using resting-state functional magnetic resonance imaging (rsfMRI), I aim to further understand neural network connectivity and plasticity through examining possible compensatory techniques the brain may employ when reorganization is required.

1.2 Resting-State Functional Connectivity

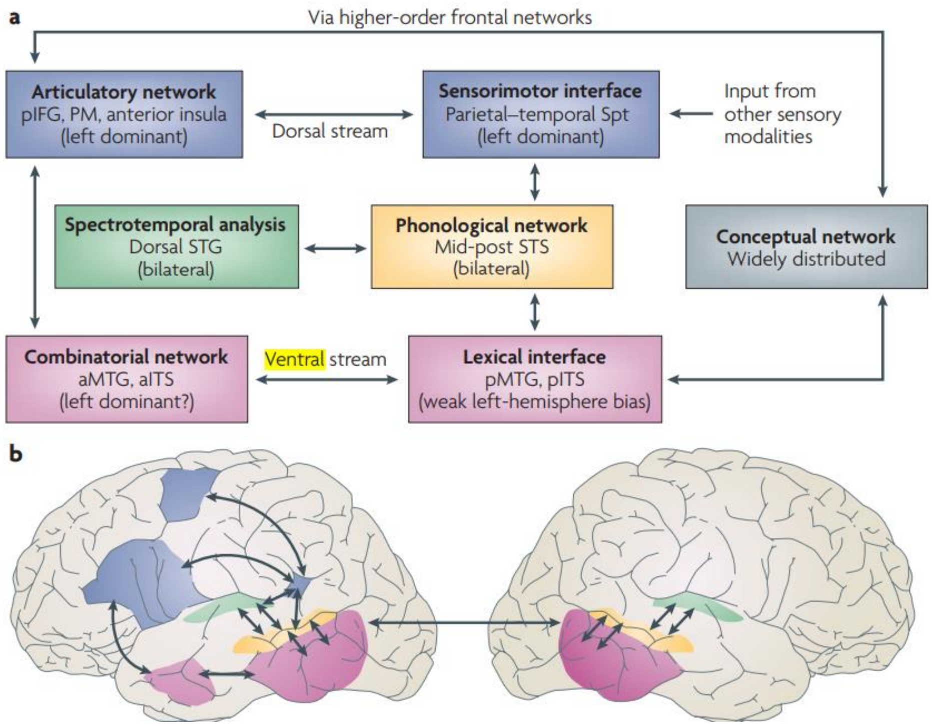
Networks of interest are typically defined using resting-state MRI and calculating a FC measure between core nodes. Resting-state FC is defined as the temporal alignment of brain signals from differing brain regions while the brain is at baseline or at rest (Beckmann et al.2005). Higher correlation of signals from differing brain regions indicate "spatially distributed networks," (Beckmann et al., 2005). This current study will utilize resting-state data to investigate intrinsic neural connectivity differences between the case study participant and neurotypical control participants.

1.3 Bilateral Language Networks

When investigating the effects of AgCC on neural connectivity, language networks can provide significant insight because of their bilateral nature. Hickok and Poeppel (2007) propose that the left lateralized dorsal stream supports speech production and the bilateral ventral stream supports speech comprehension. Hinkley et al. (2016) showed that while neurotypical controls display lateralized left hemisphere activations during language use, AgCC patients showed more right hemisphere activation. These findings suggest that with the absence of the corpus callosum, language network reorganization may occur. Because language is a complex, higher-order cognitive skill supported by numerous different brain networks, further investigation is needed to determine how changes in language network reorganization may influence connectivity in other brain regions (Zhu et al., 2014).

Figure 1

Dual Stream Model of Language



Note. This figure was obtained from Hickok and Poepell (2007).

1.4 Default Mode Network

The default mode network is often associated with an internally-oriented state and its activity typically decreases during goal-directed tasks. However, numerous studies have shown that the default mode network is highly multifunctional (Smallwood et al., 2021). Smallwood et al. (2021) theorized that the topographical location of the default mode network informs its function. The default mode network is thought to be located at the end of large-scale networks' processing streams, and thus may serve to integrate and temporally align incoming signals from different networks. It may also play a role in “predictive coding,” (Smallwood et al., 2021). This is the process of monitoring neural activity in order to identify and reduce mismatch between expected signals and observed signals (Smallwood et al., 2021). This monitoring role of the default mode network may be significant when considering the possibility that in the absence of a corpus callosum, more reliance may be placed on monitoring mechanisms to support higher-order cognitive processes (Smallwood et al., 2021).

1.5 Frontoparietal Control Network

The frontoparietal control network is an externally-guided network that includes the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), and the cortex along the intraparietal sulcus (IPS). Although it is known to support functions such as awareness and attention, it is also associated with control functions that are thought to support efficient and meaningful language communication (Hertrich et al., 2021). In particular, the DLPFC serves numerous functions related to language processing such as integration of prosody, discourse management, inference making, and error repair (Hertrich et al., 2021). The left frontoparietal network has been described as a language-cognition related brain network, but the right frontoparietal also plays a role in language processing (Zhu et al., 2014). For example, the right DLPFC seems to be involved in management of error awareness, switching languages in bilingual speakers, and contributes to the processing of literal sentences (Hertrich et al., 2021).

1.6 Previous Research

Decreases in interhemispheric connectivity is common in patients after a callosotomy, supporting the role of the corpus callosum in synchronizing neural activity (Mancuso et al., 2019). However, disruption of global interhemispheric FC is not typically as pronounced in patients with AgCC as it is in split-brain or callosotomy patients. This suggests there may be some neural reorganization (i.e., alternative pathways of information transfer) that takes place during developmental years to support normal ranges of interhemispheric connectivity (Mancuso et al., 2019). Compared to controls, variability is most often seen in regional/network connectivity. Although some studies show sustained interhemispheric connectivity within the default mode network, others support reduced connectivity. For example, the posterior cingulate cortex specifically has shown disrupted interhemispheric FC as a result of AgCC (Owen et al., 2013). Reductions in FC are not wholly unsurprising considering that this network is known to be disrupted in many conditions such as major depressive disorder, Alzheimer's disease, autism spectrum disorder, or in the presence of brain tumors (Luo et al., 2011; Mancuso et al., 2019; Tordjman et al. 2021). A study by Sharp et al. (2011) found that higher levels of diffuse axonal injury within the corpus callosum was associated with lower FC in the default mode network in patients with traumatic brain injury. Although this population differs from the one examined in this study, the findings support that structural alterations of the corpus callosum can impact default mode network functional connectivity.

Studies investigating the frontoparietal network in AgCC have resulted in varying conclusions as well. One notable study found normal levels of FC during easy tasks, but reduced interhemispheric and intrahemispheric connectivity when the complexity of the task was increased (Hearne et al., 2019, Mancuso et al., 2019). On the other hand, a study by Owen et al. (2013) found altered connectivity between the left and right frontoparietal regions, despite normal global connectivity. This finding supports that even though global connectivity may be undisrupted, effects of AgCC may be more pronounced in associative regions (Mancuso et al., 2019). Findings of frontoparietal network connectivity differences resulting from resting-state fMRI are minimal.

1.7 Research Goals

This present study will investigate how intrinsic neural connectivity of two core networks, one internally oriented (i.e., default mode network) and one externally oriented (i.e., frontoparietal network), are affected in in the absence of a corpus callosum. Furthermore, it will examine functional connections between these networks and bilateral language networks to identify any potential compensatory mechanisms enacted to support normal levels of language and cognition. The current study contains the following hypotheses:

Default Mode Network:

1. Based on previous findings from corpus callosum agenesis patients, and how frequently default mode network interhemispheric connectivity is disrupted in other disorders, default mode network interhemispheric connectivity is expected to be disrupted.

Frontoparietal Network:

2. The AgCC subject will display normal interhemispheric connectivity within the frontoparietal network based on previous studies that have shown undisrupted connectivity during easy tasks.
3. The AgCC subject will display altered intrahemispheric connectivity. Specifically, there may be decreased FC in the left frontoparietal network due to possible reliance on the right frontoparietal network for functions such as error awareness and literal sentence comprehension.

Frontoparietal, Default Mode, and Language Networks:

4. In the AgCC subject, both the default mode network and the frontoparietal network (specifically, the dorsolateral prefrontal cortex nodes) will display increased FC with the dual language stream as a compensatory mechanism to support normal language function. This is expected due to recent research supporting the roles of both the dorsolateral prefrontal cortex and the default mode network as regions of the brain involving error awareness and self-monitoring of neural activity.

CHAPTER 2

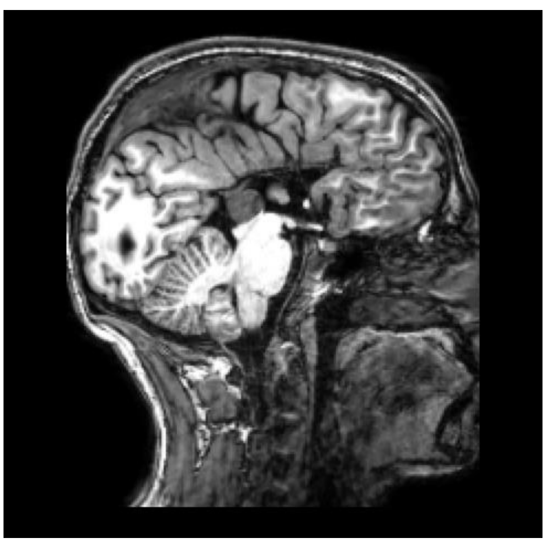
METHODS

2.1 Participants

Case subject: Resting-state fMRI data was obtained from a male individual with congenital agenesis of the corpus callosum. Anterior and posterior commissures remain intact. The participant was 28 years old at the time of data collection and had 12 years of education. He is a native English speaker and is left-handed. He is typically functioning and does not display medical, lingual, or social deficits. There is no history of head trauma, neurological disease, or psychiatric disruptions. He is referred to as CS1001 in this study. Figure 2 displays CS1001's structural MRI scan.

Figure 2

Case Study Structural MRI



Normal Control Group: 30 neurotypical adults with ages ranging from 18 to 64 with no history of head trauma, neurological disease, or psychiatric disturbances were recruited. Tables 1 and 2 report demographic statistics of the control group.

Table 1

Control Group Demographics by Sex

	Frequency	Percent
Female	23	76.7
Male	7	23.3

Table 2

Control Group Mean Age and Education

	Mean	St. Deviation
Age	32.03	16.88
Education (Years)	15.8	2.25

This study was approved by Arizona State University's Institutional Review Board and consent was obtained from all participants. Participants were compensated for their participation via cash, gift cards, or extra credit in an undergraduate course.

2.2 Image Acquisition

Resting-state MRI data were obtained using the 3T Phillips Ingenia MRI scanner equipped with a 32 channel radiofrequency head coil located at the Keller Center for Imaging Innovation at the Barrow Neurological Institute in Phoenix, Arizona. A T1 image was collected with the following parameters: FOV = 270 × 252, TR = 6.74 s, TE = 3.10 ms, flip angle = 9, voxel size = 1 × 1 × 1 mm. Resting-state fMRI data were acquired using single-shot EPI with following parameters: one 10-min run, 197 total volumes, TR = 3000 ms, FOV = 217 × 217, matrix = 64 × 62, 3.39 mm slice thickness, in-plane resolution = 3.39 × 3.39 mm.

2.3 Data Analysis

2.3.1. MRI data preprocessing.

For all resting-state fMRI data was preprocessed using Statistical Parametric Mapping 12 (https://www.fil.ion.ucl.ac.uk/spm). The first two time points of each run were discarded to ensure that the magnetization reached a steady state and the subjects adapted to the environment. Slice timing adjusted to compensate the interleaved acquisition in remaining 187 volumes. The realignment was applied to correct head motion using 6 standard head motion parameters. Then the structural image (i.e., T1) was reoriented to fit the functional image. Diffeomorphic anatomical registration through exponentiated Lie algebra normalization (DARTEL) was used to segment the structure image to white matter, grey matter, cerebral spinal fluid and normalize to Montreal Neurological Institute (MNI) template (Ashburner, 2007). Finally, using the normal parameter of structural image, the functional data were spatially normalized to MNI space. Nuisance covariates including white matter signal, cerebrospinal fluid signal, and head motion parameters were removed by using a regression technique. We also applied band-pass filtering between 0.01 and 0.1Hz and spatial smoothing.

2.3.2 Functional connectivity.

Nodes from the language network, sensorimotor network, default mode network, and frontoparietal network were included in the FC computation. Functional connectivity was computed between the different regions of interest (ROI) utilizing previous task-based fMRI research. Language network nodes were obtained from Labache et al. (2019). The study identified nodes in the dorsal and ventral streams with peak coordinates using tasks that have confirmed reliable engagement of the dorsal (speech production, word repetition) and ventral (e.g., sentence comprehension) regions of the language networks. The nodes were labeled as 6mm radius spheres around the peak coordinates. Frontoparietal and default mode network nodes were obtained from a task-based study done by Gao and Lin (2012). The Pearson correlation coefficients of core nodes were calculated and then fisher transformed. Nodes utilized in this study are listed in Table 3 and node locations are presented in Figures 2 and 3.

Table 3

Network nodes

Networks	**MNI Coordinates**	**Abbreviation**
Default Mode Network		
Ventromedial prefrontal cortex	0, 51, -7	vmPFC_DMN
Posterior cingulate cortex	1, -55, 17	PCC_DMN
Left posterior inferior parietal lobule	-47, -71, 29	L_post_inf_par_lobule (lpIPL)
Right posterior inferior parietal lobule	50, -64, 27	R_post_inf_par_lobule (rpIPL)
Frontoparietal Network		
Left anterior inferior parietal lobule	-52, -49, 47	L_ant_inf_par_lob_FP (laIPL)

Right anterior inferior parietal lobule	52, -46, 46	R_ant_inf_par_lob_FP (raIPL)
Left dorsalateral prefrontal cortex	-50, 20, 34	L_dlPFC_FP
Right dorsalateral prefrontal cortex	46, 14, 43	R_dlPFC_FP
Language Network Nodes		
Left frontal superior	-11.9, 46.5, 41.4	G_Frontal_Sup-2 (F1_2)
Left frontal inferior orbital	-42.2, 30.5, -16.9	G_Frontal_Inf_Orb-1 (F3O1)
Left frontal inferior tri	-49.4, 25.6, 4.7	G_Frontal_Inf_Tri-1 (F3t)
Left frontal insula anterior 2	-33.8, 16.8, -12.7	G_Insula-anterior-2 (INSa2)
Left frontal insula anterior 3	-33.7, 23.7, 0.6	G_Insula-anterior-3 (INSa3)
Left frontal inferior frontal	-43.1, 14.8, 29.4	S_Inf_Frontal-2 (f2_2)
Left frontal precentral	-42.2, 0.7, 49.9	S_Precentral-4 (prec4)
Left temporal supramarginal	-55.2, -51.7, 25.5	G_SupraMarginal-7 (SMG7)
Left temporal superior temporal 4	-56.5, -48.4, 13.4	S_Sup_Temporal-4 (STS4)
Left temporal angular	-37.5, -70.4, 39.5	G_Angular-2 (AG2)
Left temporal mid 3	-61.0, -35.0, -4.8	G_Temporal_Mid-3 (T2_3)
Left temporal mid 4	-53.1, -59.4, 7.0	G_Temporal_Mid-4 (T2_4)
Left temporal superior 4	-58.7, -23.3, 3.7	G_Temporal_Sup-4 9 (T1_4)
Left temporal superior temporal 1	-49.7, 14.0, -21.5	S_Sup_Temporal-1 (STS1)
Left temporal superior temporal 2	-54.9, -7.2, -12.8	S_Sup_Temporal-2 (STS2)
Left temporal superior temporal 3	-54.7, -33.0, -1.7	S_Sup_Temporal-3 (STS3)

Note. Table includes only left hemisphere language nodes. Right language nodes are homologues.

Figure 3

Left Hemisphere Network Nodes

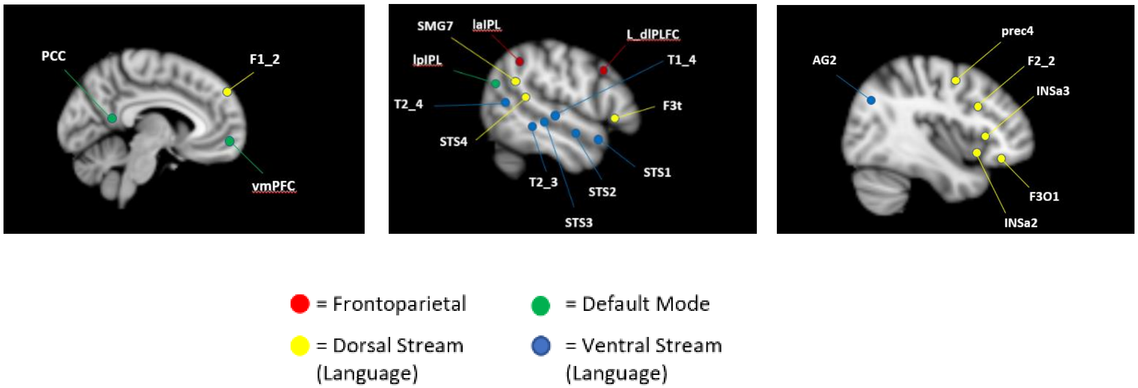
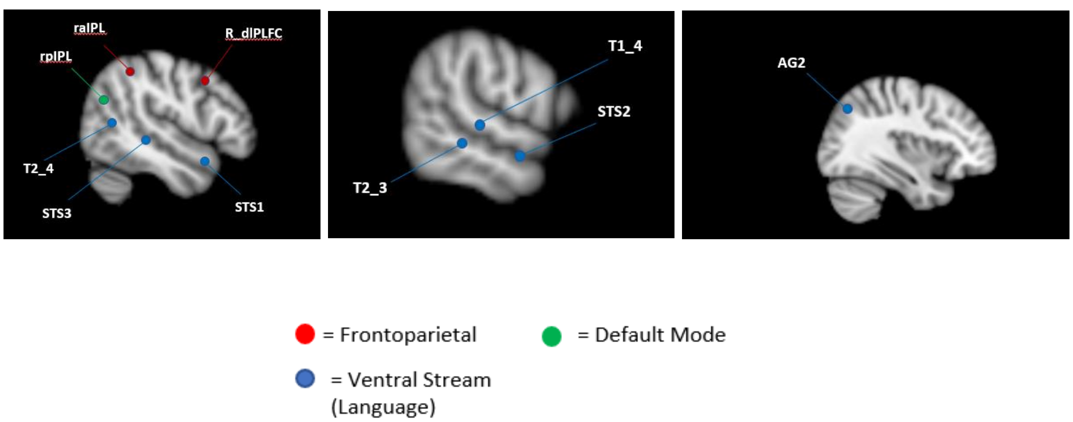


Figure 4

Right Hemisphere Network Nodes



2.3.3 Single-case analyses.

To compare between and within network functional connectivity of CS1001 (i.e., AgCC case study) and controls, Crawford et al.'s (2003) intraindividual measures of association in neuropsychology (i.e. the "IIMA.exe" applet, downloadable here: https://homepages.abdn.ac.uk/j.crawford/pages/dept/SingleCaseMethodsComputerProgra ms.HTM#iima) (Crawford et al., 2003).The program allows for comparison of correlation coefficient averages of the control group and the individual case study to determine significant differences in functional connectivity ($p < 0.05$).

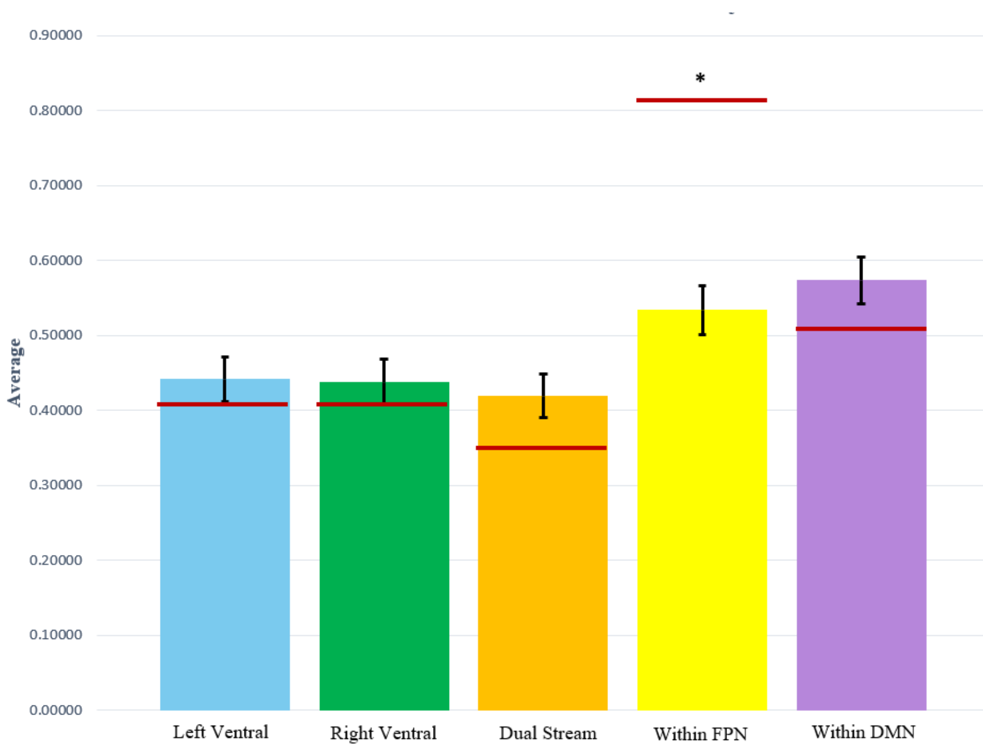
CHAPTER 3

RESULTS

CS1001 displayed significantly higher FC within the frontoparietal network (t(29)=1.84, $p<0.05$). CS1001 also displayed significantly lower FC between the default mode network and the right ventral language stream (t(29)=-1.813, $p<0.05$). In general, CS1001 displayed lower general connectivity within and between default mode and language networks, and higher general connectivity within and between frontoparietal and language networks, although these differences were not significant.

Figure 4

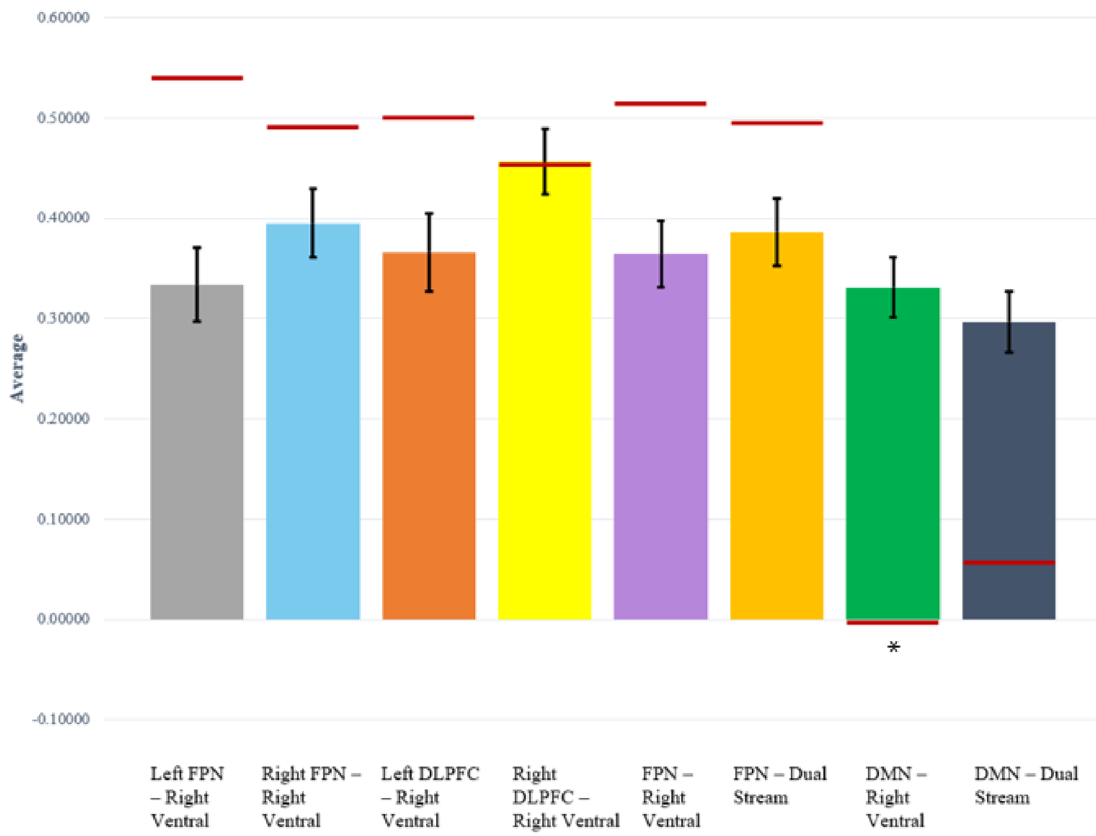
Average Within Network Functional Connectivity



Note. Red lines indicate CS1001's correlation coefficient. Asterisk indicates significant findings.

Figure 5

Average Between Network Functional Connectivity



Note. Red bars indicate CS1001's correlation coefficient. Asterisk indicates significant findings.

Table 4

Functional Connectivity Results for Within Networks

FC Measure	FC CS1001	Mean Control	Standard Deviation Control
Left Ventral	.40	.44	.16
Right Ventral	.41	.44	.17

Dual Stream	.36	.42	.16
Within Frontoparietal	.81	.54	.18
Within Default Mode	.50	.57	.17

Table 5

Functional Connectivity Results for Between Networks

FC Measure	FC CS1001	Mean Control	Standard Deviation Control
Left Frontoparietal – Right Ventral Stream	.54	.34	.20
Right Frontoparietal – Right Ventral Stream	.50	.40	.19
Left DLPFC – Right Ventral Stream	.51	.37	.21
Right DLPFC – Right Ventral Stream	.45	.46	.18
Frontoparietal – Right Ventral	.52	.37	.18

Frontoparietal – Dual Stream	.49	.39	.18
Default Mode – Right Ventral	-.002	.32	.16
Default Mode – Dual Stream	.07	.29	.16

Table 6

Single Case Statistic Results for Within ***Networks***

FC Measure	*t* value	*p* value	95% confidence interval
Left Ventral	-.29	0.39	25.38-52.77%
Right Ventral	-.26	.40	26.45-53.95%
Dual Stream	-.41	.34	21.50-48.32%
Within Frontoparietal	**1.8**	**.04**	**89.73-99.31%**
Within Default Mode	-.47	.32	19.68-46.15%

Note. Significant values in bold.

Table 7

Single Case Statistic Results for Between Networks

FC Measure	*t* value	*p* value	95% confidence interval
Left Frontoparietal – Right Ventral Stream	.94	.18	69.65-91.63%
Right Frontoparietal – Right Ventral Stream	.45	.33	53.24-79.82%
Left DLPFC – Right Ventral Stream	.56	.29	56.95-82.82%
Right DLPFC – Right Ventral Stream	-.13	.45	31.21-59.06%
Frontoparietal – Right Ventral	.76	.23	63.82-87.90%
Frontoparietal – Dual Stream	.46	.32	53.57-80.09%
Default Mode – Right Ventral	**-1.8**	**.04**	**0.76-10.67%**

Default Mode – Dual Stream	-1.3	.11	4.02-21.73%

Note. Significant values in bold.

3.1 Post-hoc Analyses and Results

Post-hoc single-case t-tests were run to further investigate differences between groups in dual stream language and frontoparietal connectivity. Right frontoparietal nodes showed greater connectivity that approached significance ($t(29)=1.699$, $p=0.05$), suggesting the higher levels of frontoparietal connectivity may be driven by the right hemisphere. No other significant differences were found within the dual stream language network.

Table 8

Functional Connectivity Results for Right Frontoparietal Network

FC Measure	FC CS1001	Mean Control	Standard Deviation Control
Right Frontoparietal	1.31	.74	.22

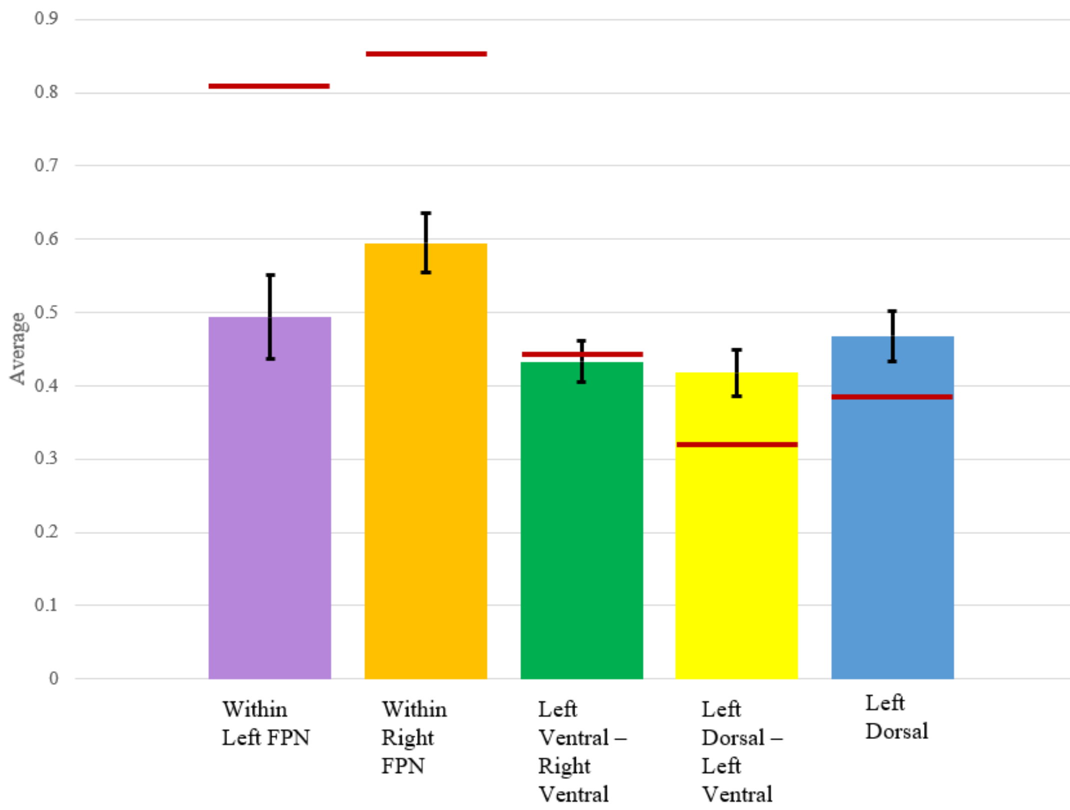
Table 9

Single Case Statistic Results for Right Frontoparietal Network

FC Measure	*t* value	*p* value	95% confidence interval
Right Frontoparietal	1.7	.05	87.53-98.90%

Figure 6

Functional Connectivity Post-Hoc Analyses



Note. Red bars indicate CS1001's correlation coefficients.

CHAPTER 4

DISCUSSION

Firstly, it is important to note that numerous previous investigations of FC in individuals with AgCC, although having larger sample sizes, commonly include individuals with comorbidities such as additional brain malformations, neurological conditions, or psychiatric disorders (Mancuso et al., 2019). This study examines an individual with AgCC with no significant comorbidities which allows us to examine the effects of the condition more clearly on within and between network FC. The hypotheses that interhemispheric connectivity within the default mode network and intraconnectivity within the frontoparietal network would show disrupted connectivity was not supported. Regardless, the FC alterations that CS1001 does present with provide insight into ways the brain is able to support normal levels of language, attention, and overall cognition in an individual with AgCC.

4.1 Undisrupted Default Mode Network Connectivity

Given the role of the corpus callosum as a core communication pathway in the brain, less synchronicity of functional signals between hemispheres is typically expected in its absence (Mancuso et al., 2019). The default mode network has shown to be easily affected in a number of disorders and conditions, and FC of this network has been shown to be correlated with white matter integrity (Luo et al., 2011; Mancuso et al., 2019; Sharp et al., 2011; Tordjman et al. 2021). However, literature presents conflicting findings regarding how core networks are affected in individuals with AgCC. For example, a study by Rane et al. (2013) found significant disruptions in both the default mode and visual network; however, it must be noted that this case study individual was also diagnosed with schizophrenia, a potential confounding variable. An independent component analysis (ICA) study in 2011 also found altered connectivity of frontoparietal and default mode network nodes of individuals with AgCC, but preserved global connectivity (Seeley et al., 2007; Uddin, 2015). Contrastingly, Tovar-Moll et al. (2014) examined a group of individuals with varying corpus callosum abnormalities (i.e., complete CC agenesis, partial CC agenesis, and CC hypoplasia, or thinning of the CC) and found no connectivity differences between default mode network nodes compared to control participants.

Varied findings can potentially be explained by individual variability in core networks as well as in the brain's plastic response. In contrast to split-brain patients, individuals with AgCC do not present with "disconnection syndrome," suggesting that some extent of neural reorganization may have taken place over the lifespan to help support normal ranges of functioning (Mancuso et al., 2019). Previous studies investigating the effects of commissurotomy on FC have shown that interhemispheric connectivity can remain intact and may be maintained by sparing the anterior commissure (Mancuso et al., 2019; O'Reilly et al., 2013). Furthermore, absence of posterior commissures have had an effect on interhemispheric connectivity in parietal and occipital regions, suggesting that these structures could support connectivity and that their effect on networks could be in relation to their topographical location (Mancuso et al., 2019; O'Reilly et al., 2013). As mentioned previously, CS1001 has intact anterior and posterior commissures, which may explain the maintenance of normal interhemispheric connectivity levels of the default mode network.

Other possible functional reorganization pathways were explored in a study investigating levels of activity of large-scale brain networks, including the default mode network, in children with partial AgCC, complete AgCC, and typically developing controls (Siffredi et al., 2021). Comparable activation levels were found amongst all groups. However, children with complete AgCC displayed increased activity of the cerebellum, amygdala, and hippocampus, suggesting reorganized neural pathways may be characterized by a higher reliance on subcortical structures to maintain interhemispheric connectivity (Mancuso et al., 2019; Siffredi et al., 2021).

4.2 Reduced Connectivity Between the Default Mode Network and Right Ventral Language Stream

In comparison to controls, it was hypothesized that both the default mode network and frontoparietal network would have higher FC with language networks in CS1001. Higher FC would have suggested a compensatory mechanism taken to possibly support normal levels of cognition and language seen in CS1001. These hypotheses were not supported; instead, CS1001 presented with significantly reduced FC between the default mode network and the right ventral stream of language. These networks were anticorrelated, which is not wholly unexpected as the default mode network tends to exhibit anticorrelated relationships with task-activated networks (Liu et al., 2022).

It is believed that the ventral stream of language strongly supports speech recognition and comprehension (Hickok & Poeppel, 2007). Recent studies have also proposed the default mode network as being a contributor to language comprehension as well. Liu et al. (2022) discussed a “two brain approach” in which the internally-oriented default mode network engages with externally-oriented mechanisms in order to ultimately help transform acoustic signals into mental representations during the language comprehension process. Furthermore, previous research has shown that in healthy individuals, a subnetwork of the larger default mode network displays a strong coupling to language networks (Gordon et al., 2020). This subnetwork, called the anterior lateral subnetwork, consists of the angular gyrus, superior frontal cortex, and the posterior cerebellum (Gordon et al., 2020). The angular gyrus, located in the posterior part of the inferior parietal lobules, was included as a set of core default mode network nodes in this study. Among its multiple functions, the angular gyrus is known to support semantic processing, word reading and comprehension, attention, and social cognition (Seghier, 2012). It has also been suggested that this region serves as a hub for the processing and integration of incoming signals and multisensory information, allowing for orientation to relevant stimuli in our environment (Seghier, 2012). Smallwood et al. (2021) expands on the functions of the default mode network's role in cognition in relevance to its topographical location at the end of large-scale networks' processing streams. It is argued that networks that are closer to the cortical surface use an integrative hub (i.e., the default mode network) to process and coordinate incoming information from across the cortex.

Overall, it seems that FC between the default mode network and the ventral stream of language may represent a significant pathway that supports overall cognition and comprehension. Significantly reduced connectivity in this pathway may imply possible deficits in cognition or comprehension, yet CS1001 does not present with any. This brings about the question of which areas of the brain may possibly be overcompensating to prevent or significantly limit deficits.

4.3 Increased Functional Connectivity in Frontoparietal Network

CS1001 showed overall higher connectivity between the frontoparietal network and language networks compared to controls, as well as significantly higher FC within the frontoparietal network itself. This enhanced network activity may represent the compensatory strategy used to support lower overall levels of default mode network and dual stream language network connectivity. Increased frontal network activity and integration has been found in other populations as a potential adaptive method after injury or in the presence of a neurodegenerative disease. For example, patients with Alzheimer's disease have displayed enhanced prefrontal connectivity that has coupled with decreased default mode network connectivity (Agosta et al., 2012). This relationship may reflect frontal executive regions' increased exertion to make up for any FC deficits seen in the default mode network in order to maintain "cognitive efficiency," (Agosta et al., 2012). Additionally, better language outcomes in patients with aphasia have been associated with greater frontoparietal integration (Sharp et al., 2010). Even for healthy controls, difficult listening conditions typically promote higher frontoparietal integration, suggesting more difficult tasks not only require core language networks but may require recruitment from frontal areas that are critical to control and attention (Sharp et al., 2010; Hertrich et al., 2021).

Although the frontoparietal network is primarily a control and attention network, it does offer support for language processing. It has been suggested that within frontal regions, the language system is functionally organized in a way that the more complex a task (i.e., discourse processing or pragmatic inferences), the more reliance is placed on areas in the prefrontal cortex in addition to the language network (Hertrich et al., 2021). In other words, in tasks that are perceived as difficult or extraneous, frontal areas are increasingly activated. It is possible that this mechanism is occurring at an exponential rate in cases of AgCC, where the frontoparietal network is over-engaged even at rest to support language function and cognition.

Increased activity of the right frontoparietal network in CS1001 approached significance ($t(29)=1.70$, $p = 0.05$), suggesting that the right hemisphere may be driving the significant “within frontoparietal network” results. There tends to be patterns of higher activity in the right frontoparietal network during cognitive processing relating to response to novelty, error management, and self-monitoring (Robertson, 2014). The self-monitoring component of frontal control networks is another possible explanation for increased frontoparietal activity in CS1001. Error-related activity in the left frontoparietal network is thought to play a significant role in the earlier processes of a task such as task-setting, while the right frontoparietal network plays more of a monitoring role throughout the duration of a task (Neta et al., 2015). It is possible that an enhanced self-monitoring mechanism supported by the right frontoparietal network may be compensating for observed deficits in functional connectivity and limiting notable cognitive deficiencies that might otherwise exist (Robertson, 2014).

CHAPTER 5

OTHER CONSIDERATIONS AND FUTURE DIRECTIONS

It is also important to note that CS1001 is left-handed. Handedness has shown to correlate with language lateralization, with left-handed individuals showing increased right hemisphere language activation (Knecht et al., 2000). However, CS1001 did not display significant FC differences within language networks when compared to controls. Another study by Tejavibulya et al. (2022) found significant differences in whole-brain functional organization between left- and right- handed individuals. Largest differences were found in the prefrontal lobe; with right-handed individuals showing greater connectivity in frontal regions and left-handed individuals showing greater connectivity in posterior regions (Tejavibulya et al., 2022). These findings conflict with the those of the present study in that CS1001 presented with significantly increased connectivity in frontoparietal regions. In other words, CS1001 did not display significant differences in regions that have shown to be most affected by handedness. However, if possible, it may be useful for future studies to account for handedness.

Previous AgCC research explains variability in findings and suggests that results be interpreted with caution for numerous reasons. Firstly, it has been suggested that significant FC differences, both globally or regionally, may correlate with cognitive deficits of the individual (Hinkley et al., 2012). The lack of cognitive deficits in CS1001 may explain why there are limited significant FC differences between groups. An interesting area to explore would be to compare FC of individuals with AgCC both with and without cognitive deficits to explore this theory further.

Furthermore, differences in imaging methods could be to blame for seemingly contradicting findings in previous literature. For example, both electroencephalography (EEG) and magnetoelectroencephalography (MEG) have been more successful at identifying FC alterations when compared to fMRI. For example, a study by Zhou et al. (2014) investigated interhemispheric connectivity findings of rats after a callosotomy. Altered FC was found using EEG, but not with fMRI ICA (Zhou et al., 2014). Perhaps using EEG to discriminate between frequency bands could be a potential complementary method to fMRI (Mancuso et al., 2019).

CHAPTER 6

CONCLUSION

This study aimed to investigate how agenesis of the corpus callosum, a structure that typically supports communication between hemispheres, may promote functional reorganization to support typical levels of cognition. Using resting-state fMRI, it was found that CS1001 displayed significantly decreased FC between the default mode network and the right ventral language stream, and significantly increased FC within the frontoparietal network. As seen in other populations with varying neurological abnormalities, increased reliance on the frontoparietal network may be the mechanism that compensates for regional decreases in other networks. Increased FC in this region, particularly in the right hemisphere, may imply an overworking of self-monitoring systems.

Structural connectivity is thought to underlie functional connectivity, while FC is thought to underlie cognition (Mancuso et al., 2019). However, investigations such as these suggest that effective FC pathways can persevere in regional areas despite deviances in structural connectivity (Mancuso et al., 2019). Future studies should further investigate the potential relationship between cognitive deficits and FC, focusing primarily on frontoparietal regions. Using complementary imaging methods such as EEG would also provide a more holistic image of the effects of AgCC on the brain.

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